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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/088,801	BRENNAN ET AL.	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3-22-07, 11-21-06 and 8-30-06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-63,67,71-116,118-121 and 124-131* is/are pending in the application.

4a) Of the above claim(s) *56-63,67,71-114,119,124 and 125* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *115,116,118,120,121 and 126-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and election of species, with traverse, filed March 22, 2007, have been entered.

   Claim 130 has been amended.

   Claim 131 has been added.

   Claims 56-63, 67, 71-116, 118-121 and 124-131 are pending.

2. Applicant's election of the species "IL-6, TNF and IL-2" as the combination of cytokines to be used in producing "T_{ck} cells", with traverse, is acknowledged. Applicant traverses on the grounds that the other claimed combinations of cytokines are sufficiently closely related that the should all be examined together.

   Applicant's argument is found convincing.

   Thus, upon reconsideration, the species of combination of cytokines to be used in producing "T_{ck} cells" have been rejoined, and the species of combination of cytokines to be used in producing "T_{ck} cells" under examination are as follows: "IL-6, TNF and IL-2"; "IL-6, TNF and IL-15" and "IL-15".

   Accordingly, claims *115, 116, 118, 120, 121, 126-131 are under consideration* as they read on a method of identifying a compound with efficacy in the treatment of chronic inflammatory disease comprising pre-incubating T_{ck} cells, or T_{ck} and T_{tcr} cells, with a compound to be tested, wherein the compound is being tested for its ability to inhibit the production of the species "TNFα", and wherein the T_{ck} are produced by incubation of T cells with the combination of cytokine species: "IL-6, TNF and IL-2"; "IL-6, TNF and IL-15" and "IL-15".

   Moreover, claims 56-63, 67, 71-114, 119, 124, and 125 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

3. This Office Action is in response to applicant's amendment to the claims and election of species, with traverse, filed March 22, 2007, applicant's amendment to the abstract filed November 21, 2006, and applicant's amendment to the claims filed August 30, 2006.

   The rejections and objections of record can be found in the previous substantive Office Action on the merits, mailed February 27, 2006.

   The previous objections to the specification and claims have been withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. §§ 102(b) and 103(a) have been withdrawn in view of applicant's amendment to the claims.

New Grounds of Rejection are set forth below necessitated by applicant's amendment to the specification and claims.

4. Claim 115 and dependent claims thereof, are objected to because they recite the abbreviations "T_{ck}" and "T_{tcr}" without first writing out the phrase that these abbreviations stand for in full, which according to the instant specification is "cytokine stimulated T cells" and "T-cell receptor-stimulated T cells," respectively (see, instant specification, paragraph bridging pages 3-4).

   Applicant is required to specifically recite the full phrase followed by the abbreviation in parenthesis where it first appears in the claims to particularly identify the meaning of this abbreviation.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

   > The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 127 and 128 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

   This is a New Grounds of Rejection/New Matter rejection necessitated by Applicant's amendments to the claims filed March 22, 2007 and August 30, 2006.

   Claim 127 and 128 comprise the following step: "(i) incubating separate cultures of T_{ck} cells and T_{tcr} cells with a compound to be tested ***either during or after the activation of said T cells,...***" (emphasis added).

   In support of these claims applicant points to previous claim 68.

   However, it is not clear that the specification or claims as filed provide a sufficient written description or sets forth the metes and bounds of this phrase. The specification does not provide blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as they are currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description

requirement of the first paragraph of 35 U.S.C. 112.

Applicant is claiming a subgenus not sufficiently supported by the specification or claims as-filed. In particular, claim 68 as filed recites, "(i) pre-incubating separate cultures of T_{ck} cells and T_{tcr} cells with a compound to be tested ***either prior to fixation*** or ***during their activation***...," and the passage from the instant specification that appears to be most relevant to this limitation also indicates that the T_{ck} and T_{tcr} cells are to be incubated with the compound to be tested ***either prior to fixation*** or ***during their activation*** (see, in particular, instant specification, page 13, 2nd).

Thus, neither the specification or claims as-filed support the currently claimed species "either during or after the activation of said T cells".

A generic or a sub-generic disclosure cannot support a species unless the species is specifically described.

It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Since the instant claims recite limitations which did not appear in the specification as filed, they introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office action.

Alternatively, applicant is invited to provide sufficient written support for the limitations indicated above. See MPEP 714.02 and 2163.06

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 115, 116, 118, 120, 121 and 126-131 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This is a New Grounds of Rejection/New Matter rejection necessitated by Applicant's amendments to the claims filed March 22, 2007 and August 30, 2006. However, it should be noted that some of the issues under 35 U.S.C. § 112, 2nd paragraph presented below were essentially stated in the previous substantive Office Action on the merits of February 27, 2006.

A. "Selectively inhibit": Claims 115, 116, 118, 120, 121, 126 and 129-131

Claims 115, 116, 118, 120, 121, 126 and 129-131 are rejected under 35 U.S.C. 112, 2nd paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

In particular, the instant claims recite "a method of identifying a compound...by testing the compound for an ability to ***selectively inhibit*** the ability of T_{ck} cells to induce pro-inflammatory...wherein an ability to ***selectively inhibit*** said cytokine release..." (emphasis added).

However a method involving identifying a compound that "selectively inhibit the ability of T_{ck} cells" requires a step where the test compound is applied to something other than T_{ck} cells to screen out those test compounds which fail to selectivity inhibit T_{ck} cells.

B. "use of monocytes in the method": Claims 115 and dependent claims thereof

Claims 115, and dependent claims thereof, are rejected under under 35 U.S.C. 112, 2nd paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

In particular, claims 115 and dependent claims thereof recite "a method of identifying a compound...[that inhibits] the ability of T_{ck} cells to induce pro-inflammatory cytokine release ***from a monocyte***...comprising...(iii) co-culturing the T_{ck} cells with monocytes; and (iv) assaying for the production of pro-inflammatory cytokines ***by the monocytes***..." (emphasis added).

However a method involving "co-culturing the T_{ck} cells with monocytes" and then "assaying for the production of pro-inflammatory cytokines by the monocytes" requires a step which enables the skilled artisan to distinguish monocyte produced cytokines from T_{ck} cell produced, e.g., a step where the T_{ck} cells are fixed prior to mixing the T_{ck} cells with the monocytes so that only the monocytes are capable of producing cytokines.

C. "to a greater extent": Claim 127 and dependent claims thereof

Claim 127 and dependent claims thereof are indefinite in the recitation of, "wherein the ability of a compound to inhibit T_{ck} cell-induced production of TNFα by monocytes ***to a greater extent*** than T_{tcr} cell-induced production..." (emphasis added) because the phrase "to a greater extent" is a relative phrase which renders the claim indefinite. The phrase "to a greater extent" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention based on the recitation of this phrase alone.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 115, 116, 118, 120, 121, 126 and 129-131 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sebbag et al. (Eur. J. Immunol. 1997 Mar;27(3):624-32, of record) in view of McInnes et al. (Immunol. Today. 1998 Feb;19(2):75-9, of record) (see entire documents).

This is a New Grounds of Rejection necessitated by Applicant's amendments to the claims filed March 22, 2007 and August 30, 2006.

Sebbag teaches a model of cognate interaction between antigen-independent cytokine stimulated T-cells and monocytes/macrophage in the rheumatoid synovial membrane in which "T cells may be stimulated by, and act in conjunction with cytokines found in the RA synovial tissue to induce production of the pro-inflammatory monokine TNF-α." (see, in particular, Abstract and Introduction, pages 624-625 as well as discussion pages 630-631, including page 631, 1st paragraph). Sebbag further teaches that the inflammatory cytokines including IL-2, IL-6, TNF-α and IL-15 are found in the rheumatoid arthritis synovium, that combinations of these cytokines can induce T cell activation, including the combinations recited in the instant claims, and that of these cytokines, IL-15 can act alone to induce T cell proliferation, consistent with previous findings by McInnes et al. (see, in particular, Introduction, pages 624-625 as well as discussion pages 630-631, including paragraph bridging pages 630-631).

Sebbag further teaches that while antigen-specific autoimmune T cells initiate the chronic inflammatory response of rheumatoid arthritis, in the later stages of disease antigen-independent cytokine-stimulated T cells play a role in perpetuating the disease. According to Sebbag, this later stage of the disease is sustained by resting T cells being recruited to the synovium by chemotactic cytokines such as IL-15, and that these resting T cells are "subsequently stimulated at a site of antigen-specific response by cytokines such as IL-2 and IFN-γ produced by specific T cell and TNF-α, IL-6 and IL-15 and by macrophages to acquire monocyte-activating capacity, which can further amplify the on-going inflammatory response through the production of pro-inflammatory cytokine TNF-α." (see, in particular, bridging paragraph on page 631).

The reference teachings differ from the claimed invention in that it does not explicitly teach targeting antigen-independent proinflammatory processes within the synovium for therapeutic intervention in favor antigen-dependent proinflammatory processes.

However, McInnes teaches that "In the absence of a clearly defined antigen, antigen-independent proinflammatory processes within the rheumatoid arthritis synovial membrane offer the best targets for therapeutic intervention." (see, in particular page 77, left column, 1st paragraph). McInnes further teach that cytokine-mediated nonspecific activation of T cells has been observed, and provides as one example the combination of TNF-α and IL-6 as enhancing the capacity of IL-15 to induce cell-contact mediated macrophage activation, citing Sebbag, *ibid.* (see, in particular page 77, left column, 2nd paragraph).

Given the reference teachings which outline a nexus between cytokines found in the rheumatoid arthritis synovium, and the ability of these cytokines to activate T cells in an antigen-independent manner such that said T cells can induce the production of TNF-α from monocytes/macrophage, and the absence of a clearly defined antigen dependent pro-inflammatory response in the rheumatoid arthritis synovium, it would have been obvious to one of ordinary skill in the art to practice the instantly claimed invention with a reasonable expectation of success. In particular, it would have been obvious to one of ordinary skill in the art to use the cytokine stimulated T cells of Sebbag as means to screen for compounds which block the cognate interaction of the cytokine stimulated T cells of Sebbag with monocytes using the Materials and Methods described by Sebbag.

One of ordinary skill in the art would have been motivated to do so given the teachings of McInnes that antigen-independent proinflammatory processes within the rheumatoid arthritis synovial membrane offer the best targets for therapeutic intervention and further given the teachings of Sebbag that glutaraldehyde fixed, cytokine activated T cells can be used to model the cognate interaction between antigen-independent activated T cells and monocytes/macrophage as it occurs in the synovial membrane. It would have been further obvious to test antibodies against various T cell surface proteins to determine if they can effectively inhibit the Tck induced production of monocyte TNF-α given that, as is well known to one of ordinary skill in the art, antibodies to T cell surface proteins are readily available.

Given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. Claims 127 and 128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sebbag et al. (Eur. J. Immunol. 1997 Mar;27(3):624-32) in view of McInnes et al. (Immunol. Today. 1998 Feb;19(2):75-9) as applied to claims 115, 116, 118, 120, 121, 126 and 129-131 above (see entire documents),

and further in view of Parry et al. (J. Immunol. 1997 Apr 15;158(8):3673-81, of record)(see entire document).

This is a New Grounds of Rejection necessitated by Applicant's amendments to the claims filed March 22, 2007 and August 30, 2006.

The teaching of Sebbag and McInnes are given above.

In addition to the teachings of Sebbag given above, Sebbag further teaches that IL-10, a functional inhibitor of TNF-α, is abundantly produced by both macrophage and T cells in rheumatoid arthritis synovial tissue and plays an important role in compensatory anti-inflammatory response in the rheumatoid arthritis joint (see, in particular, page 624, Introduction, 1st paragraph). More particularly, with respect to IL-10, Sebbag teaches that, in contrast to cytokine stimulated T cells, "the observation that monocytes do not secrete detectable IL-10 in response to T cell contact-mediated signals was surprising in light of previous studies which have shown that TNF-α plays an important role in monocyte IL-10 production, citing inter alia, Parry et al., *ibid.* Sebbag further teaches that T cells themselves also secrete IL-10 in response to a signal through the T cell receptor (see, in particular, page 603, right column, 2nd paragraph).

The reference teachings differ from the claimed invention in that it does not explicitly teach identifying a compound that selectively inhibits the monocyte TNF-α inducing activity of cytokine stimulated T cells in favor of T cell receptor stimulated T cells.

However, Parry teaches that glutaraldehyde fixed T cells activated by conventional techniques either directly involving or mimicking T cell receptor stimulation induce monocyte IL-10 production and enhance LPS-induced monocyte IL-10 production (see, in particular, Introduction and Materials and Methods, pages 3673-3675 and page 3679, left column, 2nd paragraph). Parry further teaches that "IL-10 has been used in a randomized control trial in healthy volunteers, in which it was shown to be safe, to have inhibitory effects on T cells, and to suppress production of TNF-α and IL-1, with a view to its use as an immunotherapeutic for inflammatory conditions such as chronic rheumatoid arthritis..." (see, in particular, page 3734, Introduction, 1st paragraph).

Given the reference teachings concerning the therapeutic importance of IL-10 in inhibiting the production of TNF-α in the synovium by monocytes/macrophage, and further given the ability of T cells activated via the T cell receptor directly or via T cell receptor mimetics to both secrete IL-10 themselves, and to induce the secretion of IL-10 from monocytes/macrophages via cell to cell contact, it would have been obvious to one of ordinary skill in the art to practice the instantly claimed method of selecting a compound that selectively inhibits Tck cells in favor of Ttcr cells. In particular, one of ordinary skill in the art would have been motivated to set up such an assay system given the need to identify compounds that block the ability of cytokine-induced, antigen-independent T cells to induce monocyte TNF-α production in the rheumatoid arthritis synovium, wherein said cytokine stimulated T cells do not induce monocyte IL-10 secretion, balanced with the competing need to not inhibit antigen-dependent T cell receptor activated cells which are capable of production of the anti-inflammatory cytokine IL-10.

Furthermore, since both Parry and Sebbag teach the use of glutaraldehyde fixed cytokine stimulated or T cell receptor stimulated T cells to induce monocyte TNFα production one of ordinary skill in the art would have had a reasonable expectation of success in performing a side-by-side comparison of the ability of a compound to affect the ability of these fixed T cells to induce monocyte production of TNF-α.

Given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. No claim is allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
June 11, 2007

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6/11/07